

REMARKS

Claims 1-7, 9, 11-15, 17, 19, 21-24, 26-30, 34, 36, 39, 42-43, 51, 52, 60-62, and 75-84 are pending. Claims 1-3, 7, 9, 11, 13-15, 21, 22, 24, 26, 52, 60, 75-77, and 80-82 have been amended. Claims 4, 5, 17, 36, 39, 42, 61, and 62 are original. Claims 6, 12, 19, 23, 27-30, 34, 43, 51, 78, and 79 have been previously presented. Claims 83 and 84 are new. Claims 8, 10, 16, 18, 20, 25, 31-33, 35, 37, 38, 40, 41, 44-50, 53-59, and 63-74 have been canceled. No new matter has been introduced by the amendment.

1. Claim Objections

Claims 53-59 have been objected to. Claims 53-59 have been canceled. Accordingly, the Applicants respectfully submit that the objections are moot and should be withdrawn.

2. Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 2, 6, 7, 25, 38, 40, 44, 49, 52, and 60 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Applicants respectfully traverse these rejections based on the following remarks.

Claim 2 has been amended to particularly point out that the steps as recited in claim 2 are performed before the crystallization target forms the crystal.

The term “plug fluids” has been replaced with “fluids”.

Regarding whether the fluids are introduced continuously or discontinuously into the microchannels, as discussed in our response to the non-final office action dated March 16, 2009, both ways are contemplated and within the scope of the claims. Plugs are formed, for example, where at least one of the first, second, and third fluids forms an interface with the first carrier fluid after the fluids contact the first carrier-fluid, where the interface has a capillary number sufficient to allow a plurality of plugs to form in the first microchannel in the first carrier-fluid, as required in claim 1.

The Examiner does not rebut the Applicants' argument but nevertheless maintains the rejection that "it is not clear, as to whether the plug-fluids are introduced continuously or discontinuously into the channels" (Office Action, page 3). Accordingly, the Applicants respectfully request that the Examiner either withdraw the rejection or reconsider the rejection in view of the Applicants' argument.

Claim 6 and amended claim 7 do not recite the term "permeable".

Claims 25, 38, 40, 44, and 49 have been canceled.

Claim 52 has been amended to read "removing the crystal from the microchannel; placing the crystal in a capillary tube; and analyzing the crystal in a the capillary tube."

Claim 60 has been amended to read "where water is evaporated from the plugs."

In view of the above, the Applicants respectfully submit that claims 2, 6, 7, 52, and 60 particularly point out and distinctly claim the subject matter which applicant regards as the invention. Accordingly, the rejections against claims 2, 6, 7, 52, and 60 should be withdrawn; and the rejections against claims 25, 38, 40, 44, and 49 are moot and should be withdrawn.

3. Claim Rejections under 35 U.S.C. § 103

Claims 1-7, 9, 11-15, 17, 19, 21-22, 24, 26-30, 34, 36, 38-44, 51-62, and 75-82 have been rejected under 35 U.S.C. § 103(a) over Weigl et al. (U.S. Pat. No. 6,409,832) in view of Chayen (J. Cryst. Growth, 1999) and any of Shaw et al. (GB 2,097,692), Lemaitre et al. (WO 98/02237), or Torkkeli et al. (Int. Conf. on Sensors and Actuators, 2001). Claim 23 has been rejected under 35 U.S.C. § 103(a) over Weigl in view of Chayen and any of Shaw, Lemaitre, or Torkkeli, and further in view of Bardell et al. (U.S. Pat. Pub. No. 2001/0048900 A1). Claims 49 and 50 have been rejected under 35 U.S.C. § 103(a) over Weigl in view of Chayen and any of Shaw, Lemaitre, or Torkkeli, and further in view of Pantoliano et al. (U.S. Pat. No. 6,569,631). The Applicants respectfully traverse these rejections based on the following remarks.

A. There Is No Reason To Combine Weigl With Chayen

The Examiner has conceded that Weigl does not disclose crystallization in plugs formed by the fluids (Office Action, page 4). The Examiner nevertheless attempted to cure this deficiency of Weigl by asserting that Chayen teaches “preferences of microbatch crystallization in *droplets suspended in oil*, which are similar to plugs separated by an immiscible carrier fluid in microfluidic channels” such that it “would have been obvious for a person with ordinary skill in the art to modify Weigl’s method of crystallization in microfluidic structures by performing crystallization in plugs instead of during stop-flow” (Office Action, page 5; emphasis added). The Examiner also asserts that “[i]n fact, one plug of the array of plugs surrounded by the carrier fluid, which can be oil, is *exactly the same* as a droplet suspended in oil” (Office Action, page 7; emphasis added).

In contrast to the Examiner’s assertions, droplets suspended in oil are different from plugs in microchannels, and there is no reason to combine Weigl with Chayen. For example, the movement, composition, size, and rapid mixing of plugs can be manipulated during crystallization by merging, splitting the plugs, or varying the size or geometry of the microchannels. Plugs may be examined individually. The concentration of reagents in the plugs can be varied. The crystallization conditions may be varied by changing the surface chemistry of the microchannels. A non-continuous gradient of concentration of reagents in an array of plugs, separated, for example, by the carrier fluid, can be created. These characteristics, described throughout the present disclosure, are either not available to droplets suspended in oil or achieved using different methods. Accordingly, the Applicants respectfully submit that *droplets suspended in oil* used in a microbatch experiment as disclosed by Chayen are not similar to *plugs formed by fluids in a microfluidic system*, and that thus Chayen does not provide a reason to modify Weigl as suggested by the Examiner. None of Shaw, Lemaitre, or Torkkeli cures the deficiency of Weigl in view of Chayen.

B. The Cited References Do Not Teach Or Suggest All The Claim Limitations

With regard to claims 1 and 2, neither of the cited references teaches or suggests “introducing into a plug-forming region of the first microchannel: 1) a first fluid

comprising a precipitant; 2) a second fluid comprising water; and 3) a third fluid comprising a crystallization target” or “introducing into a plug-forming region of the second microchannel: 1) a fourth fluid comprising a precipitant; 2) a fifth fluid comprising water; and 3) a sixth fluid comprising a crystallization target”, as required by claims 1 and 2, respectively.

With regard to independent claim 3, neither of the cited references teaches or suggests “introducing one or more second fluids into either one of: 1) the first plug-forming region; 2) a second plug-forming region of the first microchannel; or 3) a second plug-forming region of a second microchannel”, as required by independent claim 3.

C. Weigl Teaches Away From Using Plugs

Weigl discloses a microfluidic system where the fluids either form a laminar parallel flow (see Fig. 1; and column 11, line 54 to column 12, line 8) or form a homogeneous solution (see Fig. 2; and column 12, lines 9-19). When a laminar parallel flow is formed, the two fluids *flow in parallel* and do not mix other than by *mutual self-diffusion* (see column 12, lines 52-54; emphasis added). When a homogeneous solution is formed, the homogeneous solution is transported to the *entire microfluidic channel* (39) for crystallization (see column 14, lines 21-24; and Fig. 8; emphasis added).

Further, Weigl teaches that *both* the laminar parallel flow *and* the homogenous solution designs are essential for the crystallization methods (“This action [laminar parallel flow] establishes a concentration gradient in device 10, which allows for a very well defined crystallization. Solvent molecules from one stream can *diffuse* into a parallel stream containing a different solvent and particles. The change in solvent properties along *diffusion interface zones* 16, 18 can then induce crystallization or precipitation.” See column 11, line 64 to column 12, line 3; column 15, lines 36-43; emphasis added. “The protein sample and the reagent are mixed at a certain ratio, and then flow into crystallization channel 15, where a homogeneously mixed solution 22 is slowed or stopped. Crystallization will then occur inside channel 15.” See column 12, lines 14-18.)

In contrast to laminar parallel flow and mere diffusion mixing, when plugs are formed, the reagent solutions (fluids) are no longer in *parallel flow*. The resultant plugs are separated, for example, by the carrier fluids. Rapid mixing in plugs is possible, for example, via chaotic flows known as baker's transformation.

To the extent that Weigl's design requires *both* the parallel flow *and* the homogenous solution, Weigl teaches away from using plugs, as proposed by the Examiner. Put in another way, the Examiner's proposed modification to Weigl by introducing plugs to the Weigl design would prevent the formation of either a parallel flow or a homogeneous solution, thus defeating the purpose of the Weigl disclosure.

In view of the above, the Applicants respectfully submit that Weigl in view of Chayen and any of Shaw, Lemaitre, or Torkkeli do not teach or suggest all the claim limitations as recited in independent claims 1, 3, 80, and 82. Accordingly, the rejections against independent claims 1, 3, 80, and 82 are improper and should be withdrawn.

Moreover, the dependent claims are patentable since they depend from the patentable independent claims 1, 3, and 80. In addition, the Examiner fails to show how the further limitations recited in the dependent claims would be made obvious in view of the cited references.

For example, neither of the cited references teaches or suggests solvent transfer from one plug into another plug as recited in dependent claims 6 and 7.

Neither of the cited references teaches or suggests "where the one or more second fluids is introduced into at least one of the first plug-forming region and the second plug-forming region" and "where the one or more second fluids is introduced into the second microchannel of the second plug-forming region" as recited in dependent claims 9 and 11, respectively.

Neither of the cited references teaches or suggests varying flow rates as required in dependent claims 19, 21, and 22.

Neither of the cited references teaches or suggests the relative salt concentrations in the plugs of the first type and in the plug of the second plug type as recited in dependent claims 27-30.

Neither of the cited references teaches or suggests that the substrate is soaked in water or in an aqueous salt solution prior to crystal formation as recited in dependent claims 61 and 62, respectively.

Neither of the cited references teaches or suggests “where the plurality of plugs is formed in the first microchannel when the first fluid, the second fluid, and the third fluid are simultaneously introduced into the plug-forming region of the first microchannel” as recited in dependent claim 76.

Neither of the cited references teaches or suggests the capillary numbers as recited in dependent claims 78 and 79.

Also, in order to make out a *prima facie* case of obviousness, a rejection must be supported by a clear articulation of the reason(s) why the claimed invention would have been obvious. The analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007). The Federal Circuit has stated that “rejections on obviousness cannot be sustained with *mere conclusory statements*; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (*Fed. Cir.* 2006); emphasis added. See also *KSR*, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval).

Here, regarding each of the claims 1-7, 9, 11-15, 17, 19, 21-22, 24, 26-30, 34, 36, 39, 42-43, 51, 52, 60-62, and 75-82, no clearly articulated reasons are given for the obviousness rejection of each individual claim. The Applicants respectfully request that the Examiner either withdraw the rejections or support each rejection with a clearly articulated reason.

4. New Claim

New claims 83 and 84 depend from independent claim 1. Support for new claims 83 and 84 can be found in Applicants’ specification, for example, original claim 76, and Figs. 4-7.

5. Conclusion

Based on the above, the Applicants respectfully submit that the claims are in condition for allowance. If any issues remain, the Examiner is kindly invited to contact the undersigned agent to expedite allowance.

Respectfully submitted,

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